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PATENT

Docket No.: 19603/2595 (CRF D-2400)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Hempstead et al.

Serial No. : 09/830,520

Cnfrm. No. : 9715

Filed : October 28, 1999

For : METHODS FOR REGULATING  
ANGIOGENESIS AND VASCULAR  
INTEGRITY USING TRK RECEPTOR  
LIGANDSExaminer:  
Gary B. NickolArt Unit:  
1642

## DECLARATION OF JOSEPH A. MADRI UNDER 37 C.F.R. § 1.132

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, Joseph A. Madri, pursuant to 37 C.F.R. § 1.132, declare:

1. I hold a B.S. degree and an M.S. degree from St. John's University, Jamaica, New York in Biology as well as a Ph.D. in Chemistry and an M.D. from Indiana University, Bloomington, Indiana.
2. I am a Professor in the Department of Pathology at Yale University School of Medicine, New Haven, Connecticut.
3. As demonstrated in my Curriculum Vitae (attached hereto at Exhibit 1), I have extensive expertise in the area of angiogenesis. In particular, my areas of research have included angiogenesis, angiogenic growth factor biology, connective tissue biophysics, biochemistry and cell biology, vascular biology, vascular development, neurovascular development, cardiovascular development, and immunology.
4. I have reviewed the above patent application and U.S. Patent No. 5,733,871 to Alps et. al., ("Alps") and am providing this declaration to explain the why Alps' method of treating neuronal damage would not have suggested to scientists in the field that

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the trk receptor ligands, brain derived neurotrophic factor ("BDNF"), NT-3, or NT-4, would be useful in inducing angiogenesis, as described in the present application.

5. Alps relates to the treatment of neuronal damage in the central nervous system of individuals in need of such treatment. In particular, Alps relates to intravenous administration of pharmaceutically acceptable compositions of neurotrophic factors, such as bFGF, aFGF, NGF, CNTF, BDNF, NT3, NT4, IGF-I, and IGF-II, for treating or preventing neuronal damage as a consequence of ischemia, hypoxia, or neurodegeneration. Thus, Alps relates to administration of neurotrophic factors which target neurons to improve survival and limit damage.

6. Nowhere does Alps disclose inducing angiogenesis in a patient that has cardiac ischemia or a vascular disorder by administering BDNF, NT-3, or NT-4. In its examples, Alps uses focal or global ischemia models to induce neuronal damage. However, such models are used to create the symptom that Alps is interested in treating—i.e. neuronal damage. There is no indication in Alps that the underlying condition causing neuronal damage in Alps is being treated or is capable of being treated in accordance with the present application. There is also no indication that Alps is inducing angiogenesis with BDNF, NT-3, or NT-4 as in the invention of the present application. All Alps is doing with these neurotrophic factors is what was well known in the art to use them for—treating neuronal conditions.

7. The invention of the present application goes beyond the known use of such factors and involves the discovery that BDNF, NT-3, and NT-4 can be used for the very different purpose of inducing angiogenesis.

8. The factors that Alps identifies as neurotrophic factors are wide ranging and, while they include BDNF, NT-3, and NT-4, they go well beyond them. Indeed, the bulk of the experimental work set forth in Alps is with bFGF which, unlike BDNF, NT-3, and NT-4, is not a trk receptor ligand. In the sentence bridging columns 4 and 5 of Alps, it is stated that "[s]ome neurotrophic factors are also capable of promoting neurite outgrowth and glial cell and blood vessel restoration or inducing cells to secrete other neurotrophic factors (emphasis added)." However, in column 9, lines 39-49 of Alps, it is made clear that, with regard to promoting blood vessel formation, Alps is only talking about bFGF. Alps's acknowledgement that bFGF achieves angiogenesis is no surprise, because the ability of bFGF to do so was well known in 1999.

9. What was not known even when the present application was filed in 1999 was that BDNF, NT-3, or NT-4 have the ability to promote blood vessel formation.

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These molecules, at that time, were regarded as neurotrophic factors having no relevance to inducing angiogenesis. Thus, the indication in Alps (column 9, lines 42-45) that the non-*trk* receptor ligand, bFGF, is a potent "'gliotrophic' factor that promotes the proliferation of brain glial cells (including astroglia and oligodendroglia), as well as an 'angiogenic' factor that promotes the proliferation of brain capillary endothelial cells and blood vessels" was limited to bFGF. This statement would not have suggested to those in the field that BDNF, NT-3, or NT-4 are useful in promoting angiogenesis.

10. For all of these reasons, I, like others skilled in the area of angiogenesis, reading Alps would not have not have regarded it as teaching that BDNF, NT-3, or NT-4 would be useful in inducing angiogenesis.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:

7/20/04  
Joseph A. Madri, M.D., Ph.D.

7/7/04

**CURRICULUM VITAE****Name:** Joseph A. Madri**Date and Place of Birth:** May 16, 1946; New York, New York  
Married, Two children**Education:**

1959-1963 Archbishop Molloy High School, Jamaica, New York  
 1963-1967 St. John's University, Jamaica, New York, B.S. in Biology  
 1967-1969 St. John's University, Jamaica, New York, M.S. in Biology  
 1969-1973 Indiana University, Bloomington, Indiana, Ph.D. in Chemistry  
 1973-1975 Indiana University, Indianapolis, Indiana, M.D.  
 1975-1977 Resident in Anatomical Pathology, Yale-New Haven Hospital, New Haven, CT  
 1977-1980 Fellow in Pathology, Yale University School of Medicine, New Haven, CT

**Career:**

1967-1969 NSF Traineeship, St. John's University  
 1969-1970 Associate Instructor, Indiana University  
 1970-1971 Research Associate, Indiana University  
 1971-1972 Research Assistant, Indiana University  
 1972-1973 NIH Traineeship, Indiana University  
 1975 American Lung Association Student Fellowship, Indiana University  
 1975-1977 Resident, Department of Pathology, Yale University Medicine  
 1977-1980 USPHS Individual Research Fellowship Award, Yale University  
 1980-1985 Assistant Professor, Department of Pathology, Yale University School of Medicine  
 1980-1984 Co-director, Immunohistochemistry Laboratory, Department of Pathology, Yale University School of Medicine  
 1985-1991 Associate Professor, Department of Pathology, Yale University School of Medicine  
 1989 Tenure  
 1991-present Professor, Department of Pathology, Yale University School of Medicine and The Graduate School of Arts & Sciences  
 Co-director of the Reed Foundation Fellowship in Vascular Biology  
 1992-present Director of Medical Studies, Pathology  
 1992-present Founding Scientist & Member, Board of Directors, Alexion Pharmaceuticals, Inc., New Haven, CT  
 1992-2000 Chairman, External Scientific Advisory Board, Alexion Pharmaceuticals, Inc., New Haven, CT.  
 1992-1998 Member, Shrinners Hospitals Research Advisory Board  
 1994-1999 Member, Scientific Board of Directors, Genzyme Tissue Repair, Inc. Framingham, MA.

**Medical Licenses:**

Indiana	#01026304	08/06/75 to 06/30/82
Connecticut	#022381	1979 to present

**Societies and Honors:**

Sigma Xi  
 Phi Lambda Upsilon  
 American Chemical Society  
 American Association of Pathologists  
 International Academy of Pathology  
 American Society for Cell Biology  
 New York Academy of Science  
 Diplomate - American Board of Pathology 1979  
 Member, Editorial Board of "Arteriosclerosis" 1983 to 1999

Member, Editorial Board of "American Journal of Pathology" 1984 to 1992  
 Associate Editor, "American Journal of Pathology" Jan. 1992 to May 1996  
 Member, Editorial Board of "Laboratory Investigation" July, 1991 to 1995  
 Executive Editor, "Laboratory Investigation" July, 1995 to Sept., 2003  
 Member, Editorial Board of "Angiogenesis" 1997 to Present  
 Member, Editorial Board of "Endothelium" 1999 to Present  
 Associate Editor, "FASEB J." 2002 - present  
 Reviewer for the Pathology A and Pathobiological Chemistry Study Sections, The Dental Institute, The Cancer Institute, The Atherosclerosis SCOR, Senior Fellowships Special Study Section and Developmental Cardiobiology Program Projects Study Section of The National Institutes of Health at various times from 1983 to Present  
 Black Belt-First Dan, TaeKwon-Do 1991  
 Member, American Heart Association, Study Section on Vascular Wall Biology 1991-1994  
 Member, Research Advisory Board of the Shriners Children's Hospitals, 1992-1998  
 Councilor, American Society of Investigative Pathology, July, 1993 to July, 1996  
 Black Belt-Second Dan, TaeKwon-Do 1997  
 MERIT Award from NHLBI-NIH 2/99  
 Black Belt-Third Dan, TaeKwon-Do 2000  
 Chugai Award for Meritorious Mentorship & Scholarship from the Amer. Soc. Invest. Pathol., 4/2001  
 Black Belt-Fourth Dan, TaeKwon-Do 2003

#### Areas of Interest/Expertise:

Vasculogenesis & Angiogenesis  
 Biology and Biochemistry of Connective Tissues  
 Cell Biology of Endothelial and Vascular Smooth Muscle Cells  
 Cell-Matrix Interactions  
 Immunopathology  
 Light and Electron Microscopy and Immunoelectron Microscopy

**Trainees To Date:**

PostDoctoral:	37
Ph.D. Thesis:	11
M.D. Thesis:	9
Undergraduate:	20

#### Current Support:

R37-HL28373-22 <i>Current</i> MERIT Award	The Pathology of Endothelial Neovascularization Annual Direct Costs: \$297,530.00 Duration: 3/99 to 2/09 Principal Investigator: J.A. Madri Effort: 25%
RO1-HL51018-08 <i>Current</i>	Proteinase modulation during T cell-endothelial adhesion Annual Direct Costs: \$225,000.00 Duration: 4/01 to 3/05 Principal Investigator: J.A. Madri Effort: 20%
PO1-DK38979-10 <i>Current</i>	Cell and Molecular Pathobiology of Renal Disease Project 1: Renal microvascular endothelial cell differentiation Annual Direct Costs: \$139,944.00 Duration: 7/93 to 11/04 Principal Investigator: J.A. Madri Effort: 20%
PO1-NS35476-07 <i>Current</i>	Adaptive Mechanisms of Developing Brain Project 1: Cellular and Molecular Basis of Angiogenesis in the Developing Brain

		Annual Direct Costs: \$165,850.00 Duration: 2/03 to 6/08 Project 1 Principal Investigator: J. A. Madri Effort: 20%
T32 DK07556-17 <i>Current</i>	Annual	Experimental Pathobiology Training Grant Direct Costs: \$116,232.00 Duration: 7/77 to 6/07 Principal Investigator: J. S. Morrow Effort: 5%
Reed Foundation <i>Current</i>	Annual	Postdoctoral Fellowship in Vascular Biology Direct Costs: \$30,000.00 Duration: 1/92 to 06/2004 Co-Director (with Dr. L. Bell): J.A. Madri
RO1-HL51018-08 <i>Pending</i>		Proteinase modulation during T cell-endothelial adhesion Annual Direct Costs: \$250,000.00 Duration: 4/05 to 3/09 Principal Investigator: J.A. Madri Effort: 20%

**Patents:**

- |   |                         |               |
|---|-------------------------|---------------|
| 1) Genetically engineered endothelial cells exhibit enhanced migration and plasminogen activator activity | USA # 5,336,615         | Aug. 9, 1994  |
| 2) Universal Donor Cells  | USA # 5,705,732         | Jan. 6, 1998  |
| 3) Universal Donor Cells  | Europe #00114262.9-2105 | Aug. 29, 2000 |

**Publications (203)**

- Madri, J.A. Carboxypeptidase A: Solvent and ion effects. Ph. D. Thesis, Indiana University, 1973.
- Madri, J.A., Fromowitz, F.B. Amyloid deposition in immunoblastic lymphadenopathy. Human Pathol., 9: 157-162, 1978.
- Marier, R., Valenti, A.J., Madri, J.A. Gram-negative endocarditis following cystoscopy. J. Urol., 119: 134-140, 1978.
- Stenn, K.S., Madri, J.A., Roll, F.J. Migrating epidermis produces AB<sub>2</sub> collagen and requires continual collagen synthesis for movement. Nature, 277: 229-232, 1979.
- Madri, J.A., Furthmayr, H. Isolation and tissue localization of type AB<sub>2</sub> collagen from normal lung parenchyma. Am. J. Pathol., 94: 323-331, 1979.
- Roll, F.J., Madri, J.A., Furthmayr, H. A new method of iodinating collagens for use in radioimmunoassay. Anal. Biochem., 96: 489-499, 1979.
- Madri, J.A., Furthmayr, H. Collagen polymorphism in the lung: An immunochemical study of pulmonary fibrosis. Human Pathol., 11: 353-366, 1980.

8. Roll, F.J., Madri, J.A., Albert, J., Furthmayr, H. Codistribution of collagen types IV and AB<sub>2</sub> in basement membranes and mesangium of the kidney: An immunoferritin study of ultrathin frozen sections. J. Cell Biol., 85: 597-616, 1980.
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12. Kemp, J.D., Madri, J.A. The immune response to human type III and type V (AB<sub>2</sub>) collagen: antigenic determinants and genetic control in mice. Eur. J. Immunol., 11: 90-94, 1981.
13. Ingber, D.E., Madri, J.A., Jamieson, J.D. Role of basal lamina in the neoplastic disorganization of tissue architecture. Proc. Natl. Acad. Sci., 78: 3901-3905, 1981.
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22. Madri, J.A., Stenn, K.S. Aortic Endothelial Cell Migration: I. Matrix requirements and composition. Am. J. Pathol., 106: 180-186, 1982.
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54. Smith, L.T., Holbrook, K.A., Madri, J.A. Collagen types I, III and V in human embryonic and fetal skin. Amer. J. Anat., 175:507-521, 1986.
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201. Esparza, J., Kruse, M., Lee, J., Michaud, M and Madri, J.A., MMP-2 null mice exhibit an early onset and severe experimental autoimmune encephalomyelitis due to an increase in MMP-9 expression and activity. Submitted, 2004.
202. Carrithers, M., Tandon, S., Canosa, S., Michaud, M., Graesser, D. and Madri, J.A., Enhanced susceptibility to endotoxic shock and impaired STAT3 signaling in CD31- deficient mice, In Revision, 2004.
203. Biswas, P., Zhang, J., Schoenfeld, J., Schoenfeld, D., Gratzinger, D., Canosa, S., Madri, J.A., Interactions and identification of the regions of PECAM-1 involved in  $\beta$ - and  $\gamma$ -catenin associations and their biological significance, Submitted, 2004.
204. Sankar, S., Lum, J., Mahooti-Brooks, N., Centrella, M., McCarthy, T.L., Madri, J.A., Modulation of transforming growth factor beta receptor profiles differentially regulate TGF- $\beta$  mediated responsiveness in vascular endothelial cells. In Preparation, 2004.

#### **Committee Work**

Member - Department Safety Committee, 1980-1983  
 Member - Housestaff Selection Committee, 1980-1987 & 1989-1993  
 Member - Medical Student Pathology Course Committee, 1980-Present  
 Member - Graduate Student Program Committee, 1983-Present  
 Member - MD/PhD Student Advisory and Admissions Committee, 1986-Present  
 Member - Miles Seminar Series Program Committee, 1984-1986  
 Chairman - Pathology Department Research Seminar Series Committee, 1981-1987  
 Chairman - Departmental Medical School Thesis Committee, 1982-1985  
 Chairman - Departmental Photographic Services Committee, 1985-1987  
 Director of Graduate Studies, Experimental Pathology, 1986-1987  
 Member - American Cancer Society Institutional Research Grant Review Committee, 1988-1990  
 Member - FASEB-AAP Program committee, 1988-1990  
 Chairman - Pathology Search Committee - in Pediatric & Neonatal Pathology, 1989-1990  
 Co-Chairman - Yale University Center of Molecular Medicine Cardiobiology Advisory Group, 1989-1991  
 Member - Yale University Planning & Priorities Committee, 1990 - 1993  
 Director of Medical Studies: Pathology - 1992- Present  
 Member - Yale University Basic Sciences Curriculum Subcommittee - 1992 - Present  
 Member - Yale University Education Policy & Curriculum Committee - 1996 - 1998  
 Councilor - American Society of Investigative Pathology, 7/1/93 to 6/30/96  
 Member - ASIP Committee on Career Development, Women & Minorities, 7/1/93 to 6/30/96  
 Member - Pathology Department Executive Committee, 2/99 to present  
 Member - Yale University Senior Appointments and Promotions Committee, 1999 - 2002  
 Chair - Anna Fuller Foundation Fellowship Selection Committee at Yale, 2000 - Present  
 Member - ASIP Meritorious Awards selection committee, 2002 to present

### **Presentations at National and International Meetings:**

Gordon Conference - Structural Macromolecules. Collagen. Speaker, "Endothelial Cell Collagen Biosynthesis: Structure/Function Relationships." Santa Barbara, CA, 2/80.

Gordon Conference - Structural Macromolecules. Collagen. Speaker, "Monoclonal Antibodies to Type IV Collagen: Molecular Probes." Plymouth, NH, 7/81.

FASEB Symposium Chairman & Speaker. "Immunochemistry of the Extracellular Matrix." New Orleans, LA, 4/82.

Symposium, The Extracellular Matrix: Chemistry, Biology, Pathology. Speaker, "Collagen Immunology and Immunochemistry." Washington University, St. Louis, 6/82.

Conference on: The biology of Inflammation, Cell-Cell Interactions and Connective Tissue: Potential New Approaches to Atherosclerosis Research. Speaker, "Endothelial Cell-Matrix Interactions in Hemostasis and Angiogenesis." NIH, Washington, DC, 9/82.

Gordon Conference - Atherosclerosis. Speaker, "Endothelial Cell-Matrix Interactions: The Role of Matrix in Angiogenesis." Meriden, NH, 6/83.

Gordon Conference - Structural Macromolecules - Collagen. Speaker, "Capillary Endothelial Cell Cultures: Phenotypic Modulation by Extracellular Matrix." Plymouth, NH, 7/83.

CIBA Foundation Symposium. Basement Membranes and Cell Movement. Speaker, "The Structure and Organization of Basement Membranes." London, U.K., 1/84.

FASEB Symposium - Matrix Aspects of Wound Healing. Speaker, "The Role of Matrix in Modulating the Angiogenic Response." St. Louis, MO, 4/84.

Biology of the Vascular Endothelial Cell: Third International Symposium. Speaker, "Endothelial Cell Cytoskeletal-Matrix Interactions." Boston, MA, 6/84.

Cellular and Molecular Organization of Epithelia, British Society of Cell Biology. Speaker, "Endothelial cell-Matrix Interactions in Large Vessel and Microvascular Endothelium." Kent, England, 9/84.

Biology, Chemistry and Pathology of Collagen, N.Y. Academy of Sciences Symposium. "Endothelial Cell-Extracellular Matrix Interactions." New York, NY, 10/84.

FASEB Symposium Co-Chairman & Speaker. "Plasma Membrane Interactions with the Cytoskeleton and Exoskeleton." Anaheim, CA, 4/85.

Histochemical Society Annual Meeting, Invited Lecture: "Endothelial Cell-Matrix Interactions: In Vitro Models of Angiogenesis." Washington, DC, 5/85.

Gordon Conference - Atherosclerosis. Speaker, "Endothelial Cell Proteoglycan Sulfate Metabolism: Modulation by Matrix." Meriden, NH, 6/85.

Gordon Conference - Structural Macromolecules. Collagen. Chairman & Speaker - Session on The Pathology of Connective Tissues. Plymouth, NH, 7/85.

NIH Symposium on: Perspectives in Endothelial Cell Biology. Speaker, "Cytoskeletal-Matrix Interactions of the Endothelium." Washington, DC, 12/85.

FASEB Symposium Chairman & Speaker. "Extracellular Matrix-Cytoskeleton-Membranes." St. Louis, MO, 4/86.

George Washington University Sixth Annual International Spring Symposium: Cardiovascular Disease '86: Molecular and Cellular Mechanisms, Prevention, Treatment. Speaker, "The Extracellular Matrix as a Modulator of Neovascularization." Washington, DC, 5/86.

University of Iowa, Pulmonary Disease Division, Boehringer-Ingelheim Lecturer, Iowa City, Iowa, 11/6-7/86.

Gordon Conference - Cell Contact and Adhesion Speaker, "Endothelial Cell-Matrix Interactions: Microvascular Endothelial Cells." Tilton, H.H., 6/87.

Distinguished Lecture Series, The Cellular and Molecular Biology Component of ASEND, University of North Dakota, Lecturer, "Microvascular Endothelial Cells: Modulation by Extracellular Matrix." Grand Forks, N.D., 9/27-29/87

Tissue Culture Association Annual Meeting, Invited Lecture: "Interactions of Soluble (TGF- $\beta$ ) and Solid Phase (Matrix) Factors in Angiogenesis." Las Vegas, NV, 6/12-15/88.

Gordon Research Conference on Vascular Cell Biology, Speaker, "Endothelial Cell Modulation by Solid Phase (Matrix) and Soluble Factors (TGF- $\beta$ )." Meridian, N.H., 7/31/88 - 8/5/88.

Vth Workshop of The Swiss Association Against High Blood Pressure, "The Vascular Smooth Muscle Cell". Lecture Title: "Interactions of Soluble and Solid Phase Factors in Arterial and Capillary Endothelial Cells". Montreux, Switzerland, 10/2/88 - 10/4/88.

FASEB Symposium Chairman & Speaker. "Adhesive Proteins and Matrix Interactions in Vascular Cells" New Orleans, LA, 3/89.

AASLD Asilomar Conference on Connective Tissue Biology of the Liver. Speaker, "Endothelial cell responses to injury: Modulation by matrix and soluble factors" Asilomar, CA, 4/16 to 4/19/89.

Biology and Chemistry of Transforming Growth Factor Beta, N.Y. Academy of Sciences Symposium. Speaker, "The Effects of TGF- $\beta$ 1 and  $\beta$ 2 on Vascular Cells" Bethesda, MD, 5/18 to 5/20/89.

Workshop on the Biology of the Renal Microvasculature, Speaker, "Cell-Basement Membrane Interactions in Control of Growth and Differentiation" National Institutes of Health, Bethesda, MD, 10/23/89 to 10/24/89.

Endothelial Cells in Development and Disease, Speaker, "Regulation of Endothelial Cell Function by Extracellular Matrix", National Institutes of Health, Crystal City, VA, 11/19/89 to 11/21/89.

The Biology of Sarcomas, UCLA symposium, Co-organizer, Session Chairman and speaker "Interactions of tumor cells, host stromal cells and the extracellular matrix", Lake Tahoe, CA, 3/11/90 to 3/16/90.

The Endothelial Cell/Tissue Engineering, Joint UCLA symposia, Joint meeting, Session Chairman and speaker "Endothelial cell phenotypes" Keystone, CO, 4/6/90 to 4/12/90.

First Altschul Symposium, Atherosclerosis: Cellular and molecular interactions in the artery wall, Organizing committee member and Speaker, "Soluble factor and matrix modulation of vascular cell phenotype", Saskatoon, Saskatchewan, Canada, 4/29/90 to 5/2/90.

American Lung Assoc., American Thoracic Society World Conf. on Lung Health, Invited speaker in Cellular and extracellular regulation of pulmonary vascular growth and development, "Extracellular matrix composition and organization as a modulator of microvascular endothelial cell phenotype, Boston, MA, 5/20/90 - 5/24/90.

Second Gordon Research Conference on Vascular Cell Biology, Session chairman and Speaker on vascular cells and extracellular matrix, "Vascular Cell Phenotypic Modulation by Solid Phase (Matrix) and Soluble Factors." Meridian, N.H., 7/29/90 - 8/3/90.

Workshop on "Development of Cell Lines for Hypertension Research" Invited Speaker, "The role of the extracellular matrix and soluble factors in modulating vascular cell behavior", National Institutes of Health, Bethesda, MD, Feb. 19 & 20, 1991

FASEB Symposium Co-Chairman & Speaker. "Cell-Cell Interactions in Vascular Cells" Atlanta, GA, April, 1991.

24<sup>th</sup> Annual Lofland Conference, Speaker: Speaker, "Positive and Negative Modulators of Endothelial Cell Migration", Seattle, WA, May 22 to 26, 1991.

International Society of Nephrology Sponsored Symposium "Forefronts in Nephrology - Biology of the Glomerular Mesangium", Co-Organizer and Speaker, "Matrix-Driven Growth Factor Receptor Modulation of Vascular Cells", Kloster Banz, F. R. Germany, June 9 to 12, 1991.

MCDB/ISU Symposium on Transforming Growth Factor- $\beta$  and Related Proteins in Development, Speaker: "Modulation of Vascular Cell Behavior by Transforming Growth Factors- $\beta$ ", Ames, Iowa, September 20 to 23, 1991.

The Molecular Biology of the Endothelial Cell, UCLA symposia, Joint meeting, Session Chairman and Speaker "Endothelial cell phenotypes" Keystone, CO, 1/13/92 to 1/17/92.

American Heart Association Meeting on Vascular Cell Biology, Speaker, "Fibronectin alternate splicing in vascular cells: Functional Significance", SnowBird, Utah, 1/29/92 to 2/1/92.

FASEB-APS Society Symposium Speaker. Cellular and Molecular Biology of the Endothelial Cell, "The inter-relationships between growth factors and extracellular matrix components in angiogenesis and neovascularization", Anaheim, CA, April 5 to 10, 1992.

Third Gordon Research Conference on Vascular Cellular and Molecular Biology, Meeting Co-Chairman and Speaker, "The role of PECAM-1 (CD31) in modulating endothelial cell migration", Meridian, N.H., 6/29/92 to 7/3/92.

Upjohn Brook Lodge Workshop Speaker, "A new understanding of the role of matrix metalloproteinases in tumor biology", Invited Participant, Augusta MI, 9/27/92 to 9/29/92.

Biology of the Vascular Endothelial Cell: VII International Symposium on the Biology of Vascular Cells. Speaker, "Endothelial Cell-Matrix Interactions." San Diego, CA, 11/10/92 to 11/14/92.

American Heart Association, 10<sup>th</sup> National Conference on Thrombosis and Hemostasis, Speaker, "Factors that enhance and inhibit endothelial cell migration", New Orleans, LA, 11/18/92.

Cell Adhesion Mechanisms in Leukocyte Traffic, UCLA symposia, Joint meeting, Session Chairman and Speaker "Microvascular Endothelial cell Differentiation" Keystone, CO, 1/24/93 to 1/31/93.

Tissue Regeneration Workshop, Invited Speaker, "Extracellular Matrix Modulation of Endothelial Cell Phenotype During Angiogenesis", Princeton, NJ, Johnson & Johnson, 3/9 & 10/93.

Endothelial Changes in Age-Related Vascular Disease Workshop, National Institute on Aging, Invited Speaker, "Matrix Organization and Endothelial Differentiation", Bethesda, MD, 4/26 & 27/93.

American Heart Association, Conference on Molecular and Cellular Biology of Vascular Cells, Speaker, "The Role of T cell Proteinases in Transmigration", Boston, MA, 10/15/93 to 10/17/93.

Molecular Biology of the Endothelial Cell, UCLA symposia Speaker, "Microvascular Endothelial cell Differentiation" Keystone, CO, 1/16/94 to 1/23/94.

FASEB-ASIP Society Symposium Speaker. Tissue Repair and Regeneration, "The role of c-src in endothelial cell signal transduction during migration and angiogenesis", Anaheim, CA, April 24 to 29, 1994.

FASEB-ASIP Society Symposium Co-Chairman & Speaker (with Dr. Marlene Rabinovitch). Extracellular Matrix in the Vessel Wall, "Extracellular Matrix Mediated Signalling in Vascular Cells Following Injury", Anaheim, CA, April 24 to 29, 1994.

Fogarty International Center Conference on TGF- $\beta$ s: Biological Mechanisms and Clinical Applications, Speaker, "The Modulation of Vascular Cells by TGF- $\beta$ s", Nat'l. Institutes of Health, Bethesda, MD., May 4-6, 1994.

4<sup>th</sup> Gordon Research Conference on Vascular Cellular and Molecular Biology, Speaker, "Engagement of  $\alpha\beta 1$ /VCAM-1 Elicits T cell Proteinase Induction during Transmigration", Meridian, N.H., 6/13/94 to 6/19/94.

2nd Franz Volhard Symposium on "Mechanisms of Angiogenesis", Speaker, "Cell-Matrix Interaction in Angiogenesis" Max-Delbrück Center, Berlin, Germany, 5/25/95 to 5/28/95.

Gordon Research Conference on Cell Adhesion, Speaker, "Specific integrin mediated signalling", Andover, N.H., 6/11/95 to 6/15/95.

Gordon Research Conference on Matrix Metalloproteinases, Speaker, "Engagement of  $\alpha\beta 1$ /VCAM-1 Elicits T cell Proteinase Induction during Transmigration", Andover, N.H., 7/16/95 to 7/21/95.

International Symposium: New Frontiers in Infection, Inflammation and Autoimmunity, Speaker, "Integrin-Mediated Proteinase Induction: Its role in T cell Transendothelial Migration", Atezelsberg Castle, Erlangen, Germany, 11/30/95 to 12/3/95.

Wound Healing in Context/Tissue Engineering, UCLA symposia, Joint meeting, Session Chairman and Speaker "Extracellular matrix modulation of Microvascular Endothelial cell TGF $\beta$  receptor expression" Taos, NM, 1/23/96 to 1/28/96.

American Association for Cancer Research Special Conference: Proteases and Protease Inhibitors, Speaker "The roles of adhesion molecules and proteinases in lymphocyte transendothelial migration", Panama City, FL, 3/2/96 to 3/5/96.

FASEB-NAVBO/ASIP Society Symposium Co-Chairman & Speaker (with Dr. Tim Hla). Vascular Cell and Molecular Biology, "Extracellular Matrix Mediated Signalling in Vascular Cells", New Orleans, LA, 5/31/96 to 6/4/96.

Sixth World Congress for Microcirculation, Session Co-chairman and Speaker: The Extracellular Matrix as a Modulator of Vascular Growth - "Modulation of Endothelial Cell Phenotype by Matrix", Munich, Germany, 8/25/96 to 8/29/96.

Twelfth International Symposium on Cellular Endocrinology "The Extracellular Matrix: Its Synthesis, Function and Degradation", Speaker: "Adhesion molecules and proteinases in T cell transendothelial migration", Lake Placid, New York, 9/12/96 to 9/15/96.

Second International Symposium on the Etiology and Pathobiology of Transplant Vascular Sclerosis, Chair & Speaker, Plenary Session IV: Cell-Matrix Interactions, "Extracellular Matrix Modulation of Vascular Cell Behavior", Bermuda Southampton Princess Resort, Bermuda, 3/5-3/9/97.



Gordon Research Conference on Angiogenesis and Microcirculation, Speaker, "Matrix-driven integrin-mediated PECAM-1 tyrosine dephosphorylation during vasculogenesis and endothelial cell migration" Salve Regina College, Newport, RI, 08/17/97 to 08/22/97.

Thirteenth International Symposium on Cellular Endocrinology "The Development of the Vascular System", Speaker: "PECAM-1 (CD31) tyrosine phosphorylation and signaling in vasculogenesis and angiogenesis" Lake Placid, New York, 9/11/97 to 9/14/97.

Cardiovascular Function Symposium, American Heart Association, Speaker: "The role of PECAM-1 in vasculogenesis and angiogenesis" Lake Tahoe, CA, 2/22/98 to 2/25/98.

Endothelium/Molecular Mechanisms of Leukocyte Trafficking, Joint UCLA symposium, Speaker "Vascular differentiation during post-natal neural development", Lake Tahoe, CA, 3/21/98 to 3/28/98.

NHLBI/ATS Workshop on the Molecular and Genomic Effects of Tissue Oxygen Deprivation in Sleep Apnea. Speaker: "Hypoxia-Induced Brain Angiogenesis", Bethesda, MD, 9/24/98 to 9/25/98.

University of Toronto, Faculty of Medicine, Department of Laboratory Medicine and Pathobiology, Keynote Speaker, Research Day, Toronto, Canada, 2/1/99.

International Society for Heart Research Symposium, Speaker: "PECAM-1 and Angiogenesis", San Diego, CA, 6/9/99 to 6/12/99.

Gordon Research Conference on Angiogenesis and Microcirculation, Poster Presenter, "PECAM-1 is a reservoir for and a modulator of  $\beta$ -catenin" Salve Regina College, Newport, RI, 08/15/99 to 08/20/99.

New York Academy of Medicine conference: Angiogenesis-Research Frontiers, Invited Speaker: "Differential tyrosine and serine phosphorylation of endothelial PECAM-1 modulates association with  $\beta$ - and  $\gamma$ -catenins and SHP-2: Implications for angiogenesis", New York City, NY, 1/10/00.

FASEB-ASIP Society Symposium Speaker. Symposium: Regulation of Vascular Cell Growth by Extracellular Matrix, Lecture Title: "PECAM-1: A modulator of junctional, adhesive, migratory and proliferative activities", San Diego, CA, 4/14/00 to 4/19/00.

FASEB-ASIP Society Chugai Award Recipient and Invited Chair & Speaker. Chugai Symposium: Lecture Title: "PECAM-1: A multidomain/multifunctional protein with diverse signaling and scaffolding properties - Implications for angiogenesis and inflammation", Orlando, FL, 3/31/01 to 4/4/01.

University of Illinois, Chicago, Medical School, DeTrana Lecture in Pathology, "PECAM-1: A multidomain/multifunctional protein with diverse signaling and scaffolding properties - Implications for angiogenesis and inflammation" April 23, 2001.

Gordon Research Conference on Matrix Metalloproteinases Speaker: "Matrix Metalloproteinases and vascular control: new paradigms", Il Chocco, Tuscany, Italy, 5/13/01 to 5/18/01.

National Multiple Sclerosis Society Round Table Discussion - Invited Panelist "Strides and Stumbles in MS", Hartford, CT, 6/26/01.

FASEB-ASIP Society Symposium Co-Chair & Speaker. Proteases, Matrix and Proteoglycans: Lecture Title: "Coordinate Control of MT1-MMP and MMP-2 Expression During Angiogenesis: The roles of Egr-1, Sp1 and AP1", New Orleans, LA, 4/21/02 to 4/24/02.

Third Ringberg Conference on Molecular Mechanisms of Leukocyte Traffic, Invited Speaker, "CD31: A modulator of vascular and leukocyte function" Ringberg, Germany, 9/22/02 to 9/25/02, 2002.

American Society For Cell Biology 42<sup>nd</sup> Annual Meeting, Co-Chair and Speaker, Minisymposium: "Cell Biology of Angiogenesis", San Francisco, CA, 12/14/02 to 12/18/02.

New Therapeutic Targets in Vascular Biology, Invited speaker: "The inter-related roles of VEGF, PECAM-1 and MMP-2 in cardiac cushion development", Geneva, Switzerland, 2/6/03 to 2/9/03.

Novo Nordisk Foundation Consortium 5<sup>th</sup> Annual Conference on "Vascular Biology in Complications of Diabetes" Invited speaker; "Maternal Diabetes: Effects of on embryonic vascular development – a VEGF-A mediated process". Tammsvik Conf. Ctr., Bro, Sweden, 5/16/03 to 5/18/03.

International Society on Thrombosis and Haemostasis – XIX Congress, Invited speaker: "Cell adhesion and Angiogenesis", Birmingham, UK, 7/12/03 to 7/18/03.

FASEB-ASIP Society Symposium Co-Chair & Speaker. Molecular and cellular basis of disease: Structure and function of the extracellular matrix in disease: Novel roles and regulation of MMPs and TIMPs in disease. Lecture Title: "Evidence for a cellular protease thermostat in health and disease", Washington, DC , 4/17/04 to 4/22/04 .

XIII<sup>th</sup> International Vascular Biology Meeting, Invited Speaker, "PECAM-1 A dynamic multifunctional regulator of junctional integrity", Toronto, Canada, 6/1/04 to 6/5/04.